

⑫

EUROPEAN PATENT APPLICATION

⑳ Application number: 86810421.7

㉔ Date of filing: 25.09.86

㉑ Int. Cl.⁴: **C 07 D 487/04**

C 07 D 487/14, C 07 D 471/14,
C 07 D 495/14, C 07 D 498/14,
C 07 D 513/14, C 07 D 493/14,
A 61 K 31/505, A 61 K 31/535,
A 61 K 31/54
//(C07D487/04,249:00,239:00),
(C07D487/14,249:00,239:00,
235:00),(C07D471/14,249:00,
239:00,221:00),(C07D487/14,
249:00,239:00,209:00),
(C07D495/14,333:00,249:00,
239:00)

㉒ Priority: 30.09.85 US 782234 20.03.86 US 841886

㉓ Date of publication of application:
08.04.87 Bulletin 87/15

㉔ Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

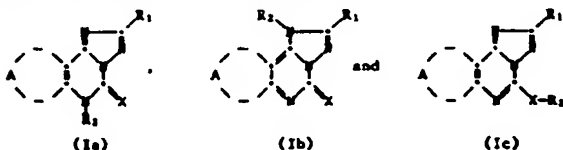
㉕ Applicant: CIBA-GEIGY AG
Klybeckstrasse 141
CH-4002 Basel (CH)

㉖ Inventor: Francis, John E., Dr.
15 Wexford Way
Basking Ridge, NJ 07920 (US)

Gelotte, Karl O.
 106 Stanle Brae Drive
 Watchung, NH 07060 (US)

㉗ 2-Substituted-*e*-fused-[1,2,4,]triazolo-[1,5-*c*]pyrimidines pharmaceutical compositions and uses thereof.

㉘ Compounds of the formulae Ia, Ib and Ic



wherein

X is O, S, NH or NR;

R is alkyl, alkenyl, alkynyl, cycloalkyl, aromatic-ring-alkyl all of which may be optionally interrupted by a hetero atom; OH; an aromatic ring; or the group -C(=NH)-NH₂;

R₁ is optionally substituted and selected from a carboxylic aromatic and a heterocyclic group which heterocyclic group is aromatic, partially saturated or fully saturated, the optional substituent of R₁ being halogen, alkyl, haloalkyl, OH, alkoxy,

hydroxyalkyl, amino, mono- or di-alkylamino, carbalkoxy, carbamoyl and alkylcarbamoyl;

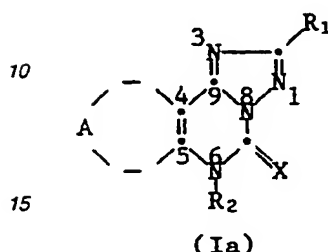
R₂ is H, alkyl, hydroxy-C₂-C₄-alkyl, alkenyl, arylalkyl, or arylalkenyl;

A is a bivalent bridging group containing chain atoms selected from C, O, N and S thus forming together with the two adjacent carbon atoms to which the chain is attached a mono- or bicyclic carbocyclic or heterocyclic group with the proviso that a monocyclic group formed by A is saturated or partially saturated and that the ring moiety adjacent to the triazolopyrimidine structure in a bicyclic, carbocyclic or heterocyclic group is other than carbocyclic aromatic, and A is optionally substituted by substituents from the group consisting of alkyl, alkoxy, hydroxy, halogen, haloalkyl, NO₂, NH₂, lower alkylthio, lower alkylsulfonyl, lower alkylsulfinyl, aryl-lower alkyl, amido, carbamoyl, carbalkoxy or aroyl; and pharmaceutically acceptable salts thereof.

Description

2-SUBSTITUTED-e-FUSED-[1,2,4]TRIAZOLO-[1,5-c]PYRIMIDINES PHARMACEUTICAL COMPOSITIONS AND USES THEREOF

The invention concerns a new e-fused [1,2,4]triazolo[1,5-c]pyrimidines, pharmaceutical compositions thereof and uses of the compounds and compositions. More particularly, the inventive compounds have the formula



its tautomers and pharmaceutically acceptable salts wherein

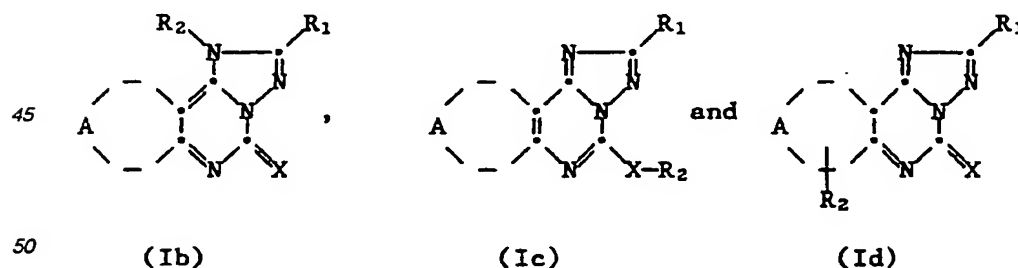
X is O, S, NH or NR;

R is lower alkyl, lower alkenyl, lower alkynyl, wherein the unsaturated bonds of the alkenyl and alkynyl groups are separated from the N atoms of X by at least one saturated carbon atom, cycloalkyl or aromatic ring-alkyl, all of the foregoing R alkyl groups being optionally interrupted by a hetero atom selected from O, N or S; or R is

OH, hydroxy-C₂-C₄-alkyl, an aromatic ring, or the group -C(=NH)-NH₂; R₁ is optionally substituted and selected from a carbocyclic aromatic and a heterocyclic group, which heterocyclic group is aromatic, partially saturated or totally saturated, wherein the optional substituent of R₁ is selected from halogen, lower alkyl, haloalkyl, hydroxy, lower alkoxy, hydroxy-lower alkyl, amino, mono- and di-lower alkyl amino, carbalkoxy, carbamoyl and alkylcarbamoyl,

A is a bivalent bridging group containing chain atoms selected from C, O, N and S thus forming together with the two adjacent carbon atoms to which the chain is attached a mono- or bicyclic carbocyclic or heterocyclic group with the proviso that a monocyclic group formed by A is saturated or partially saturated and that the ring moiety adjacent to the triazolopyrimidine structure in a bicyclic, carbocyclic or heterocyclic group is other than carbocyclic aromatic, and A is optionally substituted by substituents from the group consisting of lower alkyl, lower alkoxy, OH, halogen, halo-lower alkyl, NO₂, NH₂, lower alkylthio, lower alkylsulfonyl, lower alkylsulfinyl, aryl-lower alkyl, amido, carbamoyl, carbo-lower alkoxy or aroyl;

Other compounds within the scope of this invention are the related isomeric forms wherein the R₂ group is in another position as set forth below:



The tautomeric forms represented by the formulae Ib, Ic and Id may exist together with the form represented by formula Ia.

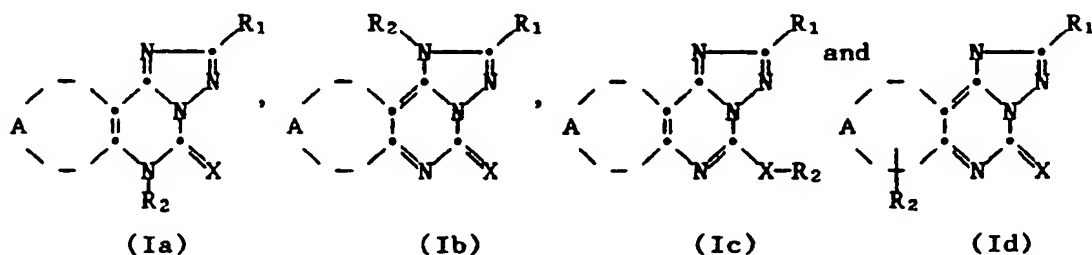
The above compounds possess benzodiazepine agonist/antagonist and anxiomodulating effects, especially when X is oxygen. In addition, and especially those compounds wherein X is mono or substituted imino, the compounds of the invention are adenosine antagonists/agonists. The benzodiazepine antagonists are primarily useful anorectic agents, CNS stimulating agents, and agents for increasing cognitive ability. They are also useful for counteracting the sedative effects of benzodiazepine tranquilizers. The benzodiazepine agonists are primarily useful as anxiolytics, CNS depressants, and anticonvulsants. Adenosine antagonists are primarily useful as anti-asthmatic agents, and may also be used in the treatment of bradyarrhythmias associated with clinical conditions such as myocardial infarction and sleep apnea. Adenosine agonists are primarily useful as antihypertensives.

Triazolo[1,5-c]pyrimidine compounds have been described in a number of references. U.S. Patent 3,045,015 discloses primarily bicyclic compounds having an unsubstituted amino group in the 2-position of the triazolopyrimidine ring. However some tricyclic rings are generically described wherein a cyclohex-1-ene ring is fused to the [e] face of the pyrimidine ring. These compounds are claimed as bronchodilators, respiratory stimulants and antiarthritic agents. In addition, antibacterial, sedative and hypotensive properties are disclosed. In J. Med. Chem. 17, 645-8 (1974), Novison concludes that the compounds in U.S. Patent 3,045,015 are active because they inhibit CAMP phosphodiesterase. Shishoo, in J. Heterocyclic Chem. 18, 43-6 (1981), reports on the synthesis of angular tricyclics which are triazolopyrimidines having a heterocyclic fused to the [e] face of the pyrimidine ring. These are unsubstituted at the 2-position of the triazolo pyrimidine ring system and have H, alkyl, aryl or arylalkyl in the same position wherein X is located in formula Ia.

Other heterocyclic rings fused to the [e] face of the [1,2,4]-triazolo[1,5-c]pyrimidine ring system are mentioned in Huang et al., Chem. Pharm. Bull. 22, (8) 1938-9 (1974); Huang et al., Tetrahedron 31, 1363-7 (1975); Leonard and Wiemar, J.O.C. 39, 3438-40 (1974); Temple et al., J.O.C. 30, 3601-3 (1965); Sauter and Stanetty, Monatsh. Chem. 106, 111-6 (1975); Brown and Shinozuka, Australian J. Chem. 34, 189-194 (1981); Bhat, Schram and Townsend, C.A. 95, 98200z (1981); Bhat and Townsend, J.C.S. perkin I, 1981, 2387-2393; Schneller and Clough, J. Heterocyclic Chem. 1974, 975-7; Sangapure and Agasimundin, Indian J. Chem. B, 1980, 115-117; Saikachi, Matsuo and Matsuda, Yakugaku Zasshi 1969, 1434-9; and Petric, Tisler and Stanovnik, Monatsh. Chem. 114, 615-624 (1983). None of these compounds possess a carbonyl, thiono or imino group at the triazolopyrimidine position 7. Further, only Saikachi et al. mentions any compound having an aryl group at the 2-position of triazolopyrimidine. No biological properties are indicated.

Since the only known compounds which have (beneficial) biological activity have the 2-position of the triazolopyrimidine ring system substituted with an unsubstituted amino group, it would be expected that such a group would be indispensable for useful biological properties to be present. Surprisingly it has now been found that replacement of that amino group with an aryl, heteroaryl, or non-aromatic heterocyclyl moiety yields biologically active compounds as well. The novel compounds of the invention are useful as anxiomodulators and benzodiazepine and/or adenosine agonists/antagonists.

The compounds of the invention all have one of the structures Ia-Ic set forth below (The ring numbering, unless stated otherwise, will be that of the triazolopyrimidine bicyclic ring structure set forth earlier.):



In the compounds according to these formulae the groups X, R₁-R₃ and A have the following preferred meanings:

X is selected from O, S, NH and N-R;

R is selected from lower alkyl, lower alkenyl, lower alkynyl, cyclo-lower alkyl, aromatic ring-lower alkyl, all of the alkyl groups being optionally interrupted by a heteroatom selected from O, N and S; an aromatic ring; and the group -C(=NH)-NH₂;

R₁ is selected from carbocyclic aromatic groups and partially saturated, totally saturated or aromatic heterocyclic groups, all of which are optionally substituted with a group selected from halogen, lower alkyl, halo (preferably fluoro) substituted lower alkyl (most preferably trifluoromethyl), hydroxy, lower alkoxy, hydroxy-lower alkyl, amino, mono-lower alkylamino, di-lower alkylamino (which alkyl groups may be the same or different), carbo-lower alkoxy, carbamoyl and lower alkylcarbamoyl; and

R₂ is selected from hydrogen, lower alkyl, hydroxy-lower alkyl, lower alkenyl, aryl-lower alkyl, aryl-lower alkenyl and aryl; preferably hydrogen.

A is a bivalent group of atoms selected from C, N, O and S, which form together with the two adjacent carbon atoms to which they are attached an optionally substituted, mono- or bicyclic aliphatic carbocyclic, or a heterocyclic ring or an optionally substituted mono- or bicyclic heteroaromatic ring, the optional substituents of which are selected from lower alkyl, lower alkoxy, hydroxy, halogen, halo (preferably fluoro)-lower alkyl, lower alkylthio, lower alkylsulfonyl, lower alkylsulfinyl, aryl-lower alkyl, amido, carbonyl, carbo-lower alkoxy and aroyl; and pharmaceutically acceptable salts thereof.

As used within this application:

The term "lower alkyl" preferably means alkyl having 1-7 carbon atoms, more preferably 1-5 carbon atoms, and most preferably 1-4 carbon atoms;

"lower alkenyl" is advantageously alkenyl having 2-7 carbon atoms, preferably 2-5 carbon atoms, and most

preferably 2-4 carbon atoms;

"lower alkynyl" is preferably alkynyl having 2-7 carbon atoms, more preferably 2-5 carbon atoms, and most preferably 2-4 carbon atoms; and

"cyclo-lower alkyl" is cycloalkyl having preferably 5, 6 or 7 ring members.

5 The aromatic ring, as used in the definition of R, is preferably phenyl, naphthyl and aromatic heterocyclyl having 5-7 members, more preferably 6 members, containing at least one heteroatom selected from O, N and S, preferably N, but not more than one O or S atom. Preferably, aromatic rings within the scope of R are 5 or 6 membered, being carbocyclic or having 1-4 nitrogen atoms, one sulfur or oxygen atom or 1-2 nitrogen heteroatoms and optionally an oxygen or a sulfur heteroatom. Such heterocyclic groups more preferably have
10 1-4 nitrogen atoms, 1 oxygen atom, 1 sulfur atom, or 1-2 nitrogen atoms together with either 1 oxygen atom or 1 sulfur atom. Preferred aromatics defined by R may be selected from phenyl, pyridyl, thienyl, furyl, pyrrolyl, tetrazolyl, pyrimidinyl and fused rings thereof wherein each of the fused ring independently meets the above limitations.

15 Although any of the groups set forth above are suitable, R is preferably lower alkyl. Also preferred are the compounds wherein X is NH.

Aromatic rings and partially and totally saturated heterocyclic groups within the scope of R₁ include phenyl, naphthyl, pyridyl, thienyl, furyl, pyrrolyl, thiazolyl, isothiazolyl, oxazolyl, imidazolyl, pyrazolyl, 1,2,3- and 1,2,4-triazolyl, tetrazolyl, pyrimidinyl, quinolyl, isoquinolyl, thienyl, pyrrolinyl, pyrrolidinyl, dihydro- and tetrahydrofuranlyl, dihydro- and tetrahydrothienyl, pyranlyl, piperidinyl, morpholinyl, pyrazolinyl, thiazolinyl, oxazolinyl, triazolinyl, and ribofuranosyl. The rings defined by R₁, when substituted, are preferably substituted
20 with lower alkyl, lower alkoxy, halogen, hydroxy, amino, carbethoxy, substituted carbamoyl, or hydroxy-lower alkyl, more preferably halogen, phenyl, halophenyl, methylaminophenyl, furanyl, and β-D-ribofuranosyl. Of the halogens, fluorine, chlorine and bromine are especially useful, with fluorine being the most preferred.

A preferably has a sufficient number of chain atoms to complete, together with the two carbon atoms of the triazolopyrimidine ring to which it is attached, a cyclohexene, cyclopentene, piperidine (especially -Δ³-piperidine), tetrahydrobenzo[b]-thiophene (especially 1,2,3,4-tetrahydrobenzo[b]thiophene), pyridine, cycloheptane, dihydropyrrole (especially 2,5-dihydropyrrole), isoxazole, oxazole, isothiazole, thiazole, pyrazole, oxthiazole, dithiazole, pyrrole, furan, thiophene, oxazine, thiazine, pyridazine, pyran, thiopyrane, oxathiin, dioxine, dithiine, pyrazine, pyrimidine or imidazole group and benzocondensated and/or partially
30 saturated benzocondensated derivatives. The aroyl substituent on A is preferably benzoyl.

Especially preferred are the compounds of formula Ia wherein (1) A is -(CH₂)₅-, X is oxygen, R₁ is 2-fluorophenyl and (2) A is -(CH₂)₄-, X is NH, R₁ is furan-2-yl. Other important compounds include those of formula Ia wherein X is oxygen, R₁ is 2-fluorophenyl and A is either -(CH₂)₄- or has sufficient chain atoms to complete a 1,2,5,6-tetrahydropyridine ring which is N-substituted with benzyl. Still other important compounds
35 are set forth in the Examples.

The claimed compounds may form acid addition salts, preferably pharmaceutically acceptable acid addition salts. The acid addition salts may be formed by the addition of inorganic or organic acids.

40 Examples of inorganic salts include halide salts, especially chlorides and sulfates. The organic acids may contain, for example, lower alkyl or aryl groups to which are attached one or more carboxy or sulfo groups. Some examples of organic salts include, for example, the acetate, methanesulfonate, toluenesulfonate, fumarate, cinnamate and benzoate salts.

The compounds of the formulae Ia-Ic and their pharmaceutically acceptable salts, and especially those wherein X represents O are benzodiazepine agonists/antagonists and anxiomodulating agents. In addition, these compounds, and especially those wherein X represents the imino or a substituted imino group, are
45 adenosine antagonists, anti-asthmatic agents, and central nervous stimulating agents; they enhance cognitive ability. These utilities manifest themselves in mammals such as human beings when administered orally, intraperitoneally or by inhalation in doses of 0.01 mg/kg to 500 mg/kg body weight, preferably 0.1 to 100 mg/kg, and most preferably 10 to 30 mg/kg.

The compounds of the invention bind to the benzodiazepine receptors and exhibit e.g. anxiolytic and/or
50 anticonvulsant effects, or antagonism of the effects of benzodiazepine drugs. Said effects are demonstrable by in vitro and in vivo tests, using advantageously mammals, e.g. mice, rats or monkeys, as test objects. Said compounds can be applied to them enterally or parenterally, advantageously orally, or subcutaneously, intravenously or intraperitoneally, for example, within gelating capsules or in the form of aqueous solutions or suspensions respectively. The applied dosage may range between about 0.1 and 100 mg/kg/day, preferably
55 between about 0.5 and 50 mg/kg/day, advantageously between about 1 and 25 mg/kg/day. The applied dosage in vitro may range between 10⁻⁵ and 10⁻¹⁰ M concentration, preferably between about 10⁻⁷ and 10⁻⁹ M.

The benzodiazepine receptor binding properties indicative of the nervous system regulatory activity of said new compounds are determined in the receptor binding assay in vitro, e.g. similarly to that in Nature 266, 732
60 (1977) or Proc. Nat. Sci. USA 74, 3805 (1977). When tritiated flunitrazepam is used, the interaction of other drugs with said receptor can be readily assessed thus: Synaptosomal membranes from rat fore-brain are incubated at 0-5° for 30 minutes with 0.5 nM tritiated flunitrazepam and various concentrations of the test substance in a buffer medium maintained at pH 7.5. Solutions of the various concentrations of the test substance are prepared by dilution of a 4.2 mM stock solution in dimethylacetamide-ethanol (1:10) with 50 mM
65 pH 7.5 Tris-HCl buffer. The membranes, containing the receptors with various amounts of tritiated

flunitrazepam, are filtered onto glass fiber filters, which are then analyzed in a liquid scintillation counter. The concentration of the compounds of this invention, required to inhibit the specific binding of 0.5 nM of tritiated flunitrazepam by 50 %, i.e. the IC₅₀, is determined graphically.

In vivo benzodiazepine receptor binding is determined essentially as described in Eur. J. Pharmacol. 48, 213 (1978) and Nature 275, 551 (1978). Test compounds in a corn starch vehicle are administered orally or intraperitoneally to mice or rats. Thirty minutes later, ³H-flunitrazepam (2 nmoles/kg in saline) is injected into the tail vein, and the animals are sacrificed 20 minutes after injection of the flunitrazepam. The brains are then assayed by determining radioactivity in a liquid scintillation counter for binding of the radioligand to the receptors. A decrease in the binding of ³H-flunitrazepam in the drug-treated animals (as compared with the binding observed in animals treated with vehicle alone) is indicative of benzodiazepine receptor binding by the test compound.

Anxiolytic effects are observed, for example, according to the Cook-Davidson conflict procedure, using male Wistar rats which are maintained at 80 % of normal body weight by dietary-, but not water restriction. They are trained to press a lever within a conditioning chamber, also containing a liquid dipper, a house light, a speaker and a grid-floor. Both lever and grid are connected to an electrical shock source and the chamber is situated in a sound-attenuated room in which a white noise-source is activated during testing, in order to mask any extraneous auditory cues. Each session of 47 minutes duration consists of two alternating schedules. The first is a Variable Interval (VI) schedule of 30 seconds, lasting for 5 minutes, during which a sweetened, condensed milk reinforcement is delivered following the first lever-press after average of 30 seconds have elapsed, and a drug induced decrement of this performance is taken as an indication of a neurological deficit. Immediately following the VI-schedule both a 1000 Hz tone and a light-cue are activated, indicating the commencement of the second Fixed Ratio (FR) schedule, lasting for 2 minutes, wherein the milk reinforcement is delivered concomitant with an electric foot shock immediately following the tenth response, thereby establishing a conflict situation. The intensity of said shock ranges between 2.0 and 3.6 mA, varying with each animal, in order to adjust them to about 25-100 responses during this schedule over the entire session. A drug-induced enhancement of performance during the FR-schedule is taken as indication of antianxiety effects. This increased performance is measured by the increased number of electric foot shocks taken during six FR sessions lasting 2 minutes each.

Anticonvulsant effects are observed, for example in the standard Metrazole (pentylentetrazole) and maximal electroshock tests for assessing anticonvulsant activity, e.g. orally in the rat.

Male Wistar rats (130-175 g) are fasted for 18 hours but allowed water as desired prior to testing. The test compound is administered in a cornstarch vehicle by oral intubation in a volume of 10 ml/Kg of body weight. One hour after administration of the test compound the animals are administered intravenously (caudal vein) a dose of 24 mg/kg of metrazole in water in a volume of 2.5 ml/kg of body weight. The rats are immediately placed in plexiglass cylinders and observed for clonic seizures of at least 5 seconds duration during the next 60 seconds. The ED₅₀ is the dose at which half the animals are protected from Metrazole induced clonic seizures during the observation periods.

Benzodiazepine antagonism is measured by the antagonism of the anticonvulsant activity of diazepam in the rat Metrazole model. Diazepam (5.4 mg/kg/po) and test compound are administered 1 hour before the Metrazole challenge.

In the maximal electroshock procedure for assessing anticonvulsant activity in rats, seizures are induced by applying 150 mA of electric current for 0.2 seconds through corneal electrodes two hours after oral administration of test compound as described for the Metrazole test above. The ED₅₀ is the dose at which half the animals are protected from electroshock induced seizures during the 5 second observation period.

The pharmacological benzodiazepine agonist and/or antagonist profile of the compounds of the invention can also be determined by measuring their effects on a rat brain membrane preparation on the displacement of ³H-flunitrazepam in the presence or absence of gamma-aminobutyric acid (GABA), on the enhancement of ³H-muscimol binding by etazolate, or on the binding by etazolate, or on the binding of ³⁵S-Butyl bicyclophosphorothionate (TBPS).

Accordingly, the compounds of the invention are useful nervous system active agents, e.g. as benzodiazepine receptor agonist/antagonists for example in the treatment or management of nervous system disorders, such as anxiety, convulsive conditions (epilepsy) or other disorders in mammals responsive to said benzodiazepine agonists/antagonists. They are also useful in the preparation of other valuable products, especially of pharmacologically active pharmaceutical compositions.

These and other methods are detailed more fully in Woods, J. Pharmacology and Experimental Therapeutics, Vol. 231, No. 3, 572-576 (1984).

Compounds which are benzodiazepine agonists include those of formula Ia wherein X is oxygen, R₂ is hydrogen, R₁ is 2-furanyl or optionally substituted phenyl and A completes a cycloheptene ring or an optionally substituted, preferably N-benzyl substituted, 1,2,5,6-tetrahydropyridine ring. Specific benzodiazepine agonists include the compounds of Example 8, 10, 11, 12 and 25.

A mixed benzodiazepine agonists/antagonist of the invention is 2-(2-fluorophenyl)-7,8,9,10-tetrahydro-[1,2,4]triazolo[1,5-c]quinazoline-5(6-H)one, set forth in Example 2.

The compounds of the invention, especially when X is imino or substituted imino, act as adenosine antagonists. Adenosine antagonism is assessed by determination of inhibition of adenosine activation of adenylate cyclase in vesicular preparations from guinea pig brains essentially as described in J. Neurochem.

22, 11031 (1974) and J. Neurochem. 38, 1437 (1982).

A specific adenosine antagonist of the invention is 5-amino-2-(2-furyl)-7,8,9,10-tetrahydro[1,2,4]triazolo[1,5-c]quinazolinemethanesulfonate.

The invention relates particularly to compounds of the formulae Ia-Ic, wherein X represents O, S, NH or NR; R is lower alkyl, aryl-lower alkyl, amino-lower alkyl, or lower alkylamino-lower alkyl, R₁ represents phenyl or phenyl substituted by one to three groups selected from lower alkyl, lower alkoxy, hydroxy, halogeno and trifluoromethyl; or R₁ represents a heterocyclic radical bonded by way of a carbon atom, said heterocyclic radical being a five or six membered ring which is aromatic or saturated either partially or totally; the heterocyclic group being unsubstituted or substituted by hydroxy, lower alkyl or halogen; and wherein R₂ represents hydrogen, lower alkyl, aryl-lower alkyl, lower alkenyl, aryl-lower alkenyl, or aryl; A is a bivalent bridging group of atoms selected from C, N, O, and S which form together with the two adjacent carbon atoms to which they are attached an optionally substituted, mono- or bicyclic aliphatic carbocyclic, or a heterocyclic ring or an optionally substituted mono- or bicyclic heteroatomic ring, the optional substituents of which are selected from lower alkyl, lower alkoxy, hydroxy, halogen, halo (preferably fluoro)-lower alkyl, lower alkylthio, lower alkylsulfonyl, lower alkylsulfinyl, aryl-lower alkyl, amido, carbonyl, carbo-lower alkoxy, and aroyl; and pharmaceutically acceptable salts thereof.

The invention more particularly relates to compounds of the formulae Ia-Ic, wherein X represents O, especially when R₂ represents phenyl or substituted phenyl, NH or NR wherein R represents lower alkyl, especially when R₁ represents an aromatic heterocyclic group or a substituted aromatic heterocyclic group, R₁ represents phenyl or phenyl substituted by one to three groups selected from lower alkyl, for example methyl or ethyl; lower alkoxy, for example methoxy; hydroxy; halogeno, for example fluoro or chloro; and trifluoromethyl; or a 5- or 6- membered aromatic heterocyclic radical bonded by way of a ring carbon atom; for example 2- or 3-thienyl; 2- or 3-furyl; 2- or 3-pyrrolyl; 2-, 3- or 4-pyridyl; 3- or 4-pyrazolyl, or 2- or 4-(imidazolyl); said aromatic heterocyclic radical being unsubstituted or substituted by hydroxy; by lower alkyl, for example methyl or ethyl; or by halogeno, for example fluoro or by chloro, R₂ represents hydrogen or lower alkyl, A has a sufficient number of chain atoms to complete, together with the two carbon atoms of the triazolopyrimidine, a cyclohexane, cyclopentene, piperidine (especially -Δ³-piperidine), tetrahydrobenzo[b]thiophene (especially 1,2,3,4-tetrahydrobenzo[b]thiophene), pyridine, cycloheptene, dihydropyrrole (especially 2,5-dihydropyrrole), isoxazole, oxazole, isothiazole, thiazole, pyrazole, oxthiazole, dithiazole, pyrrole, furan, thiophene, oxazine, thiazine, pyridazine, pyran, thiopyrane, oxathiin, dioxine, dithiine, pyrazine, pyrimidine or imidazole group and benzocondensated and/or partially saturated benzocondensated derivatives, and the optional substituents of which are selected from lower alkyl, lower alkoxy, halo-lower alkyl, aryl-lower alkyl or carbo-lower alkoxy, and pharmaceutically acceptable salts thereof.

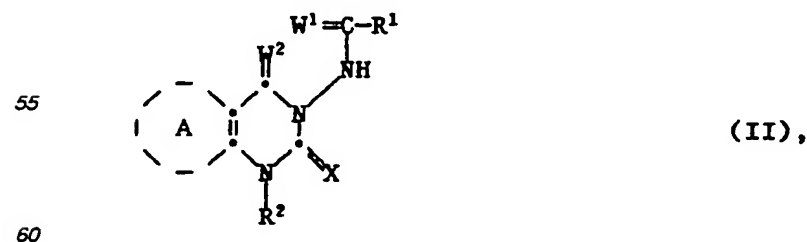
The invention relates most particularly to compounds of formulae Ia-Ic wherein R₁ represents phenyl or phenyl substituted by halogeno especially in the ortho or meta positions, particularly fluoro or chloro; or furyl, especially 2-furyl; R₂ represents hydrogen; X represents oxygen, especially when R₁ represents phenyl substituted by halogeno, for example ortho or meta fluoro; or X represents NH, especially when R₁ is 2-furyl; and A is a bivalent bridging group of atoms selected from C, N, O, and S which form together with the two adjacent carbon atoms to which they are attached a cyclohexene, cyclopentene, piperidine (especially -Δ³-piperidine), tetrahydrobenzo[b]thiophene (especially 1,2,3,4-tetrahydrobenzo[b]thiophene), pyridine, cycloheptene, dihydropyrrole (especially 2,5-dihydropyrrole), pyrazine, pyrimidine or imidazole group, and the optional substituents of which are selected from lower alkyl, lower alkoxy, halo-lower alkyl, aryl-lower alkyl or carbo-lower alkoxy, and pharmaceutically acceptable salts thereof.

The invention is especially related to the specific compounds mentioned in the examples.

The compounds of the present invention can be prepared by methods known in the prior art. In addition, compounds having formula Ia-Ic wherein X = O or S may be prepared by the following methods. The structures shown here will result in compounds of formula Ia. The corresponding products of formulas Ib-Ic can be obtained by utilizing the corresponding starting materials.

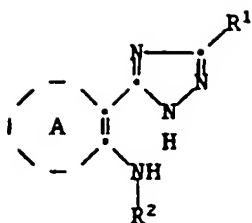
The process may consist of variations of the following steps:

a) cyclizing a compound of the formula:



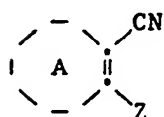
wherein R¹, R², X and ring A are as defined above, one of W¹ and W² is NH and the other one of W¹ and W² represents O or NH, by treatment with a base furnishing a nitrogen atom, or

b) cyclizing a compound of the formula:



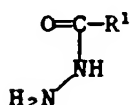
(III),

wherein R^1 , R^2 and ring A are as defined above, by treatment with a reactive derivative of carbonic acid, or
c) to obtain a compound wherein R^2 is hydrogen reacting a compound of the formula:



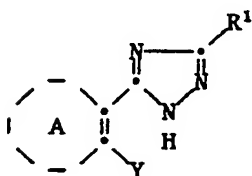
(IV)

wherein ring A is as defined above and Z is the radical of a carbonic acid derivative bonded via a nitrogen atom, with a hydrazide of the formula:



(V)

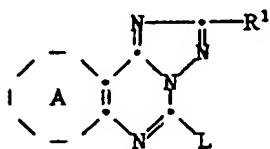
or d) to obtain a compound of formula I wherein R^2 represents hydrogen and X is oxygen, by treating a compound of the formula:



(VI),

wherein Y represents a group capable of being converted to the grouping $-N=C=O$ by an oxidizing agent, with said oxidizing agent followed by ring closure, or

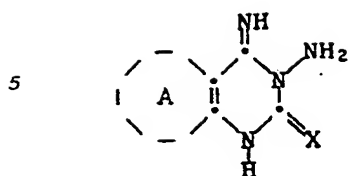
e) to obtain a compound of formula I, wherein R^2 is hydrogen and X is NH, converting a compound of the formula:



(VII),

wherein L is selected from halogen, lower alkoxy, aryl-lower alkoxy, mercapto, lower alkylthio and isothiocyanato, by replacing the group L by the grouping NH, or

f) to obtain a compound of formula I wherein R^2 represents hydrogen, by treating a compound of the formula:



(VIII)

10

with a reactive derivative of a carboxylic acid of the formula $R^1\text{-COOH}$, and if desired, converting a resulting compound into another compound of the invention and/or converting a resulting salt into the free compound or into a different salt and/or converting a resulting free compound having a salt forming group into a salt.

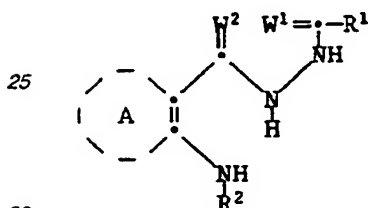
15

Process a): The base furnishing a nitrogen atom is e.g. an amine, preferably a tertiary amine, e.g. pyridine or triethylamine, but may also be ammonia.

The source of ammonia may be, for example, a carbamate, such as a lower alkyl carbamate, for example methyl- or ethylcarbamate or ammonium carbonate. Reactions may be run with or without an inert solvent at atmospheric pressure or elevated pressure, for example in a sealed tube.

20

Compounds of formula II may be prepared by treating a compound of formula



(IX),

30

wherein W^1 and W^2 independently represent O or NH with ammonia and/or with a reactive derivative of carbonic acid.

The reactive derivatives of carbonic acid include esters, amides and anhydrides of carbonic acid as well as the corresponding thio- or imino-compounds, such as, for example, phosgene, diethylcarbonate, thiophosgene, trichloromethyl chloroformate, ethyl carbamate, urea, cyanamide or guanidine.

The source of ammonia may be the same as the reactive derivative of carbonic acid, for example a lower alkyl carbamate such as ethyl carbamate.

When W^1 and W^2 represent O, compounds of the formula IX are prepared from an anthranilic ester and a hydrazide of the formula V ($R^1\text{CONHNH}_2$). When W^1 and W^2 represent NH, compounds of the formula IX are prepared from an anthranilonitrile and a hydrazidine of the formula $R^1\text{CNHNH}_2$ or a hydrazine of anthranilic

acid and a nitrile of the formula $R^1\text{CN}$. When W^1 represents NH and W^2 represents O, compounds of the formula IX are prepared from an anthranilic hydrazide and a nitrile of the formula $R^1\text{CN}$. When W^1 represents O and W^2 represents NH, IX is prepared from a hydrazidine of an anthranilic acid and a reactive derivative of the acid of the formula $R^1\text{COOH}$, e.g. a halide thereof, such as $R^1\text{COCl}$ or $R^1\text{COBr}$ or an anhydride of the formula $(R^1\text{CO})_2\text{O}$.

Process b): The reactive derivatives of carbonic acid and the general reaction conditions are those described under process a), a further reactive derivative may be a cyanogen halide, e.g. cyanogen chloride or preferably cyanogen bromide. A suitable base may be added to neutralize the hydrohalide formed during the reaction such as triethylamine, pyridine or sodium hydroxide. The cyclization preferably occurs in situ and may be catalyzed by an acid, such as mineral acids, e.g. hydrochloric acid, or a base such as a trialkylamine, e.g. triethylamine.

The compounds of formula III may be produced according to the method of Potts et al, J. Org. Chem. 35, 3448 (1970). They may also be prepared by treating a reactive precursor of an anthranilic acid, such as an

isatoic anhydride, with a hydrazidine of the formula $R^1\text{CNHNH}_2$ or by reacting a thioamide of the formula



Process c): The radical of a carbonic acid Z may be selected from isocyanato or isothiocyanato; $\text{-NHC(=O)O-lower alkyl}$ or $\text{-NHC(=S)O-lower alkyl}$; or $\text{-NHC(=O)N-di-lower-alkyl}$ or $\text{NHC(=S)N-di-lower-alkyl}$ or corresponding imido derivatives such as cyanimido (-NH-CN).

The reaction takes place preferably in an inert solvent, such as an ether solvent, for example dioxane or an alcohol solvent, for example 2-methoxyethanol, or a liquid amide, for example dimethylacetamide.

When Z represents isocyanato or isothiocyanato; or $\text{-NHC(=O)O-lower alkyl}$ or $\text{-NHC(=S)O-lower alkyl}$, the reaction may be performed in the presence of a base such as a tertiary amine, for example trimethylamine, triethylamine, and, especially, tripropylamine. The compounds of the formula IV wherein Z represents isocyanato and isothiocyanato may be converted into the corresponding compounds wherein Z represents $\text{-NHC(=O)O-lower alkyl}$ and $\text{-NHC(=S)O-lower alkyl}$, respectively, by treatment with a lower alkanol such as ethanol.

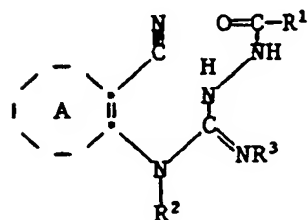
The compounds of the formula IV wherein Z represents $\text{-NHC(=O)O-lower alkyl}$ or $\text{-NHC(=S)O-lower alkyl}$ may also be formed by treating an o-aminobenzonitrile with lower alkyl chloroformate or thiochloroformate, for example ethyl chloroformate or ethyl thiochloroformate.

The compounds of the formula IV wherein Z represents $\text{NHC(=O)N-di-lower-alkyl}$ or $\text{NHC(=S)N-di-lower alkyl}$ may be formed by treating the appropriate o-isocyanatobenzonitrile or o-isothiocyanatobenzonitrile with a di-lower-alkylamine such as diethylamine.

The preferred solvents when Z represents isocyanato or isothiocyanato are ether solvents, especially dioxane and mostly preferred amides, e.g. 1-methyl-2-pyrrolidinone. The preferred solvents when Z represents $\text{-NHC(=O)O-lower alkyl}$ or $\text{-NHC(=S)O-lower alkyl}$ or $\text{NHC(=O)N-di-lower alkyl}$ or $\text{NHC(=S)N-di-lower alkyl}$ are alcohols especially 2-methoxyethanol and mostly preferred amides, e.g. 1-methyl-2-pyrrolidinone or dimethylacetamide. The reaction is preferably conducted at temperatures of 0 to 250°C, preferably 20 to 150°C.

For compounds wherein X denotes NH the starting materials needed are e.g. o-cyanimidobenzonitriles. They are described by Wentrup in Tetrahedron 27, 367 (1971) and by Bedford et al. in J. Chem. Soc., 1633 (1959).

A believed intermediate step of said cyclisation and integrated part of this process is the double cyclisation of a compound of the formula X



(X)

wherein R^1 , R^2 , R^3 and ring A are as defined above.

Process d): A group capable of being converted to the grouping -N=C=O by an oxidizing agent may be any group that is of significance for the rearrangement reactions such as Hofmann, Curtius or Lossen rearrangement, being e.g. carbamoyl, N-hydroxycarbamoyl or azidocarbonyl.

The oxidizing agent may be, for example, lead tetraacetate or a hypohalite. The hypohalite is preferably an alkali metal hypohalite such as sodium hypochlorite or sodium hypobromite. The function is believed to undergo e.g. the first stage of the Hofmann reaction (Ber. 14, 2725 (1881)), forming the isocyanate which then reacts with the free NH of the triazole.

Process e): A compound of formula VII, wherein L denotes halogen, lower alkoxy or aryl-lower alkoxy may be hydrolyzed. The hydrolysis is preferably effected by base, for example with aqueous sodium hydroxide.

The 5-halo compounds may be prepared by reacting a compound of formula I wherein X represents O with a reactive halide such as phosphoryl chloride, phenylphosphonic dichloride or phosphorous pentachloride with or without an inert solvent.

The 5-lower alkoxy or 5-aryl-alkoxy compounds may be prepared from the 5-halo compounds by treatment with the appropriate alcohol in the presence of base.

Furthermore, a 5-halo, 5-mercapto or 5-alkylmercapto group in an e-fused [1,2,4]triazolo[1,5-c]pyrimidine is displaced by ammonia or substituted ammonia to form compounds of formula I wherein X represents NR. The mercapto group may be substituted by lower alkyl, for example a methyl group, by reaction of the 5-mercapto compound with e.g. methyl chloride in the presence of a base such as sodium hydride.

The compound of formula VII wherein L represents -SCN may be treated with ammonia or an amine H_2NR , in a polar, aprotic solvent, preferably at or near room temperature. The 5-SCN compounds may be prepared from the corresponding 5-thione by treatment of the 5-thione with cyanogen bromide in the presence of a base such as, for example, sodium hydride.

Process f): A reactive derivative of a carboxylic acid of the formula $\text{R}^1\text{-COOH}$ may be selected from the corresponding acid halides, e.g. acid chlorides, acid esters, such as lower alkyl esters, iminoethers, iminothioethers, thioamides and, preferably, amidines.

The reaction may be performed in an inert solvent, such as an amide, e.g. dimethylacetamide, preferably under heating.

The starting materials of formula VIII may be prepared by reacting a compound of formula IV, wherein ring A

is as defined above and Z is selected from the groupings $-N=C=S$, $-N=C=O$, $-NC-C\equiv N$ and $-N=C=N-R^3$, with hydrazine or a reactive derivative thereof, e.g. at room temperature in an inert solvent, such as an ether, e.g. tetrahydrofuran. Said process is preferred for manufacture of compounds of formula I wherein X represents oxygen and, especially, sulfur.

Furthermore, one resulting compound of formula I may be converted into another compound of the invention. For example, the 5-thiono compounds may be converted into the 5-oxo compounds by treatment with a hypohalite salt such as sodium hypochlorite or sodium hypobromite. The 5-imino or substituted imino compounds may be hydrolyzed to the corresponding 5-oxo compound with aqueous acid. Compounds I wherein R^2 represents hydrogen and X represents oxygen may be converted to compounds wherein R^2 represents lower alkyl, for example by reaction with an alkyl halide in the presence of base, such as sodium alkoxide, in an inert solvent, such as dimethyl sulfoxide.

In the above-described preparations of the compounds of the invention, the reactions are conducted under standard conditions. For example, the reaction mixtures may be cooled or heated to appropriate temperatures, appropriate solvents and catalysts may be added, and the reaction may be conducted under an inert atmosphere.

The claimed salts and claimed neutral compounds are interconvertable. For example, acid addition salts may be converted into neutral compounds by treatment with an appropriate base, and neutral compounds may be converted into the corresponding acid addition salt by treatment with the corresponding acid.

The starting materials for the preparations of the compounds of the invention are either known or may be prepared by methods known in the art.

The compounds of formula Ia-Ic are formulated into pharmaceutical compositions comprising an effective amount of the triazolopyrimidine compounds of formula Ia-Ic or a salt thereof in combination with conventional excipients or carriers suitable for either enteral or parenteral, such as oral, bronchial, rectal or intravenous, administration. Preferred are tablets, dragées and gelatine capsules comprising the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, calcium phosphates and/or glycine, b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also, c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired, d) disintegrants, e.g. starches, agar, alginic acid or its sodium salt, or effervescent mixtures and/or, e) absorbents colorants, flavors and sweeteners. Dragée or tablet cores may be provided with suitable coatings, which may be resistant to gastric juices. Coating solutions are, for example concentrated aqueous sugar solutions, which may contain gum arabic, polyvinylpyrrolidone, polyethylene glycol, talcum and/or titanium dioxide. Resistant coatings are obtained with lacquer solutions in organic solvents, such as shellac, acetylcellulose phthalate or hydroxypropylmethyl cellulose phthalate in ethanol and the like. Dyestuffs or pigments may be added for identification of brand name and dose. Capsules are either made from hard gelatine, or they are soft, closed capsules made from gelatin and a softener, e.g., glycerin or sorbitol. The hard capsules contain either uncompressible powder mixtures, e.g. those mentioned under a) and b), or granulates similar to those used for tablets. In the soft capsules said active ingredients are preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffins or polyethylene glycols. Suppositories are advantageously solid, fatty emulsions or suspensions, containing the active ingredient, for example, in natural or synthetic triglycerides, paraffins, waxes and/or polyethylene glycols.

Compositions for parenteral administration are preferably aqueous solutions or suspensions of said active substances, but also oily solutions or suspensions thereof, e.g., in natural or synthetic fatty oils, such as sesame oil or ethyl oleate, in suitable ampoules.

Bronchial compositions are preferably aerosol sprays and may be administered from dispenser such as is described in U.S. Patents 4,292,966, 4,174,712, and 4,137,914. The active ingredient is mixed with a propellant such as a hydrocarbon, chlorofluorocarbon mixture, or carbon dioxide.

Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. They may also contain other valuable substances, and are prepared according to conventional mixing, granulating or coating methods respectively. They may contain from about 10 to 95 %, preferably from about 20 to 70 % of the active ingredient. Individual unit dosages thereof for a mammal of about 50-70 kg weight may contain preferably between about 10 and 200 mg., advantageously about 20 to 100 mg of said active ingredients.

Having generally described the invention, a more complete understanding can be obtained by reference to certain specific examples, which are provided herein for purposes of illustration only and do not limit the claims unless otherwise specified. Within the Examples, numbering of the ring systems is in accordance with the generally accepted rules of nomenclature. The temperatures are given in degrees celsius.

Examples

Example 1: A mixture of 3-(5-aminoimidazol-4-yl)-5-phenyl-1,2,4-triazole (8.5 g), trichloromethylchloroformate (7.0 g) and dioxane (400 ml) is stirred under nitrogen at 20° for 64 hours. To this is added triethylamine (5.15 ml) and the mixture stirred at 20° for 4 hours. The solid is collected, washed with water and air dried. The product is recrystallized from a mixture of dimethylformamide-ether, digested with warm methanol, filtered, washed with ether and oven dried at reduced pressure to afford 2-phenyl-1,2,4-triazolo-[5,1,-l]purin-5(6H)one as a hemihydrate, mp above 300°.

The starting material is prepared in the following way: A mixture of 6-hydrazinopurine, prepared as described by Montgomery and Holum, J. Amer. Chem. Soc. **79**, 2187 (1957), (13.5 g) diphenylether (300 ml), 1 molar p-toluenesulphonic acid in isopropanol (10 ml) and trimethylorthobenzoate (81 ml) is stirred over 2.5 hours at 180° in a apparatus containing a solvent removal trap. The mixture is cooled, diethyl ether (400 ml) added and the resulting solid stirred in hot ethanol (200 ml) for several minutes and collected. This product (12.1 g) is heated with 2.5 molar HCl in isopropanol for 18 hours at 60°, cooled, collected, washed with a little cold water and stirred 5 minutes with 10 ml of 5 % aqueous sodium carbonate solution to afford the above triazole, mp 278-280°. The hydrochloride of this product melts in the range from 324 to 326°.

Example 2: The ethyl carbamate of 3,4,5,6-tetrahydroanthranilonitrile (10 g), o-fluorobenzhydrazide (7.94 g), tri-n-propylamine (6.9 ml) and 2-methoxyethanol (170 ml) is stirred at reflux for 18 hours under nitrogen. It is cooled to room temperature and the precipitate which forms is collected, washed with ethanol and dried in vacuo. The product, 2-(2-fluorophenyl)-7,8,9,10-tetrahydro-[1,2,4]triazolo[1,5-c]quinazolin-5(6H)one, melts in the range of 266 to 268°.

The ethyl carbamate is prepared in the following way:

To a solution of sodium (43.5 g) dissolved in absolute ethanol (550 ml) is added 4-amino-3-cyano- Δ^3 -piperidine (29.1 g) and diethylcarbonate (280 ml) and the whole stirred at reflux under nitrogen for 2 hours. The solution is ice cooled and glacial acetic acid (145 ml) added cautiously followed by water (600 ml). The aqueous layer is extracted with ether several times and the extract dried over magnesium sulphate and concentrated to dryness at reduced pressure to afford an oil which gradually crystallizes. It is used without further purification (42.2 g).

Example 3: When 2-furoic acid hydroxide is substituted for o-fluorobenzhydrazide in Example 2, 2-(2-furyl)-7,8,9,10-tetrahydro-[1,2,4]-triazolo[1,5-c]quinazolin-5(6H)one is obtained as a white solid, mp 327-330° with decomposition, in 60 % yield.

Example 4: A mixture of the ethylcarbamate of 3,4,5,6-tetrahydroanthranilonitrile (8.5 g), o-methylaminobenzhydrazide (7.2 g) and 1-methyl-2-pyrrolidone (80 ml) is stirred under nitrogen at reflux for 16 hours, cooled, diluted with water (300 ml) and the precipitated solid collected, washed with water and pressed dry on the filter. It is washed with ether (100 ml) and oven dried. The free base is suspended in methanol and treated with an equimolar quantity of methanesulphonic acid. The methanesulphonate salt of 2-(2-methylaminophenyl)-7,8,9,10-tetrahydro-[1,2,4]triazolo[1,5-c]quinazolin-5(6H)one crystallizes, mp 257-260°, in 36 % yield.

Example 5: When 3-chlorobenzhydrazide is substituted for o-fluorobenzhydrazide in Example 2, 2-(3-chlorophenyl)-7,8,9,10-tetrahydro-[1,2,4]-triazolo[1,5-c]quinazolin-5(6H)one is obtained and purified by recrystallization from 2-methoxyethanol, mp 342-346° dec. in 50 % yield.

Example 6: A mixture of o-fluorobenzhydrazide (8.56 g) 1-amino-2-cyano cyclopenten-1-ylethylcarbamate (10 g, prepared as described by House et al., J.A.C.S. **84**, 3139-3147 (1962)), 2-methoxyethanol (185 ml) and tri-n-propylamine (7.4 ml) is stirred under nitrogen at reflux for 20 hours, cooled and treated gradually with water to induce crystallization. It is collected, washed with water, dried and recrystallized from ethanol to afford 8,9-dihydro-2-(2-fluorophenyl)-7H-cyclopenta[e][1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one melting in the range 251 to 253°, in 68 % yield.

Example 7: When 2-furoic acid hydrazide is substituted for o-fluorobenzhydrazide in Example 6, 8,9-dihydro-2-(2-furyl)-7H-cyclopenta[e][1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one is obtained, mp 297-299°, in 53 % yield.

Example 8: A mixture of ethylcarbamate of N-benzyl-3-cyano-4-amino- Δ^3 -piperidine (8.2 g), o-fluorobenzhydrazide (84.43 g), 2-methoxyethanol (96 ml) and tri-n-propylamine (3.9 ml) is stirred at reflux under nitrogen for 42 hours. It is cooled and the precipitated solid collected, washed with ethanol, dried and recrystallized from 2-methoxyethanol to afford pure 9-benzyl-2-(2-fluorophenyl)-7,8,9,10-tetrahydropyrido[3,4-e][1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one, melting in the range 256 to 259°. When treated with an equimolar quantity of methanesulphonic acid in methanol, the free base is converted to the methanesulphonate salt (38 %) mp 306-309° after recrystallization from 1:1 dimethylacetamide-methanol mixture.

The above ethyl carbamate derivative is prepared by the method described in Example 2 from N-benzyl-3-cyano-4-amino- Δ^3 -piperidine (Taylor et al., Tetrahedron **23**, 855-890 (1967)) and is obtained as an oil in 94 % yield.

Example 9: When the ethylcarbamate of Example 8 is replaced by N,N'-dicarbethoxy-3-cyano-4-amino- Δ^3 -piperidine, 9-carbethoxy-2-(2-fluorophenyl)-7,8,9,10-tetrahydropyrido[3,4-e][1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one is obtained, mp 307-311° with decomposition, in 46 % yield.

The bis-urethane starting material is prepared in the following way:

To a solution of sodium ethoxide in ethanol, prepared from 40.2 g of sodium dissolved in 500 ml of absolute ethanol, is added 3-cyano-4-amino- Δ^3 -piperidine (26.9 g, prepared as described by Bachmann and Barker, J. Amer. Chem. Soc. **69**, 1535 (1947)) and the whole refluxed 1 hour under nitrogen. Diethylcarbonate (105 ml) is added and the whole stirred at reflux for 2 hours under nitrogen, cooled to room temperature and glacial acetic acid (20 ml) followed by water (1.3 l) is added cautiously. The resulting solution is extracted with ether (4 x 500 ml) and the ether extracts concentrated to about 600 ml, dried over magnesium sulphate and concentrated at reduced pressure to a syrup. Trituration with ether causes precipitation of some solid and concentration of the ethereal mother liquor yields a second crop of product, mp 170-172°, suitable for further work. The yield is 68 %.

Example 10: A mixture of the ethylcarbamate of N-benzyl-3-cyano-4-amino- Δ^3 -piperidine (5.3 g), benzhydrazide (2.53 g), diethylacetamide (70 ml) and diisopropylethylamine (0.5 ml) is stirred at reflux under nitrogen for 18 hours. It is concentrated to dryness at reduced pressure, triturated with isopropanol and the resulting solid collected, dried and recrystallized from 2-methoxy-ethanol to afford pure 9-benzyl-2-phenyl-7,8,9,10-tetrahydropyrido[3,4-e]-[1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one, mp 257-259° (72 % yield).

Example 11: A mixture of the ethylcarbamate of N-benzyl-3-cyano-4-amino- Δ^3 -piperidine (10 g), p-fluorobenzhydrazide (4.41 g) and 1-methyl-2-pyrrolidone (80 ml) is stirred at reflux under nitrogen for 20 hours. It is evaporated at reduced pressure to remove most of the solvent, then diluted with isopropanol (100 ml) and stirred one-half hour. The precipitated product is collected, washed with isopropanol and dried. It is converted to the p-toluenesulphonate salt by treatment with an equimolar amount of p-toluenesulphonic acid in methanol. The salt is suspended in 2-methoxyethanol, filtered and converted back to the free base in dilute ammonium hydroxide in 42 % yield. The pure 9-benzyl-2-(4-fluorophenyl)-7,8,9,10-tetrahydropyrido[3,4-e]-[1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one melts in the range 252 to 256°.

Example 12: When 4-chlorobenzhydrazide is substituted for benzhydrazide in Example 10, 9-benzyl-2-(4-chlorophenyl)-7,8,9,10-tetrahydropyrido[3,4-e]-[1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one is obtained, melting in the range 250 to 256°, in 54 % yield.

Example 13: When 3-fluorobenzhydrazide is substituted for benzhydrazide in Example 11, 9-benzyl-2-(3-fluorophenyl)-7,8,9,10-tetrahydropyrido[3,4-e]-[1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one is obtained and purified as the methanesulphonate salt. After recrystallization from a mixture of dimethylacetamide and methanol, it melts in the range 299 to 302° and is obtained in 30 % yield.

Example 14: A mixture of N,N'-dicarboethoxy-3-cyano-4-amino- Δ^3 -piperidine (18.5 g), 2-furoic acid hydrazide (8.73 g), 2-methoxyethanol (220 ml) and tri-n-propylamine (90 ml) is refluxed under nitrogen for 18 hours. It is cooled, concentrated at reduced pressure to a thick slurry, diluted with water (500 ml), stirred for 1 hour and the solid collected, washed with methanol and air dried. The 9-carboethoxy-2-(2-furyl)-7,8,9,10-tetrahydropyrido[3,4-e]-[1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one thus obtained, (11.1 g) decomposes in the range from 316 to 320°.

Example 15: A suspension of 9-carboethoxy-2-(2-fluorophenyl)-7,8,9,10-tetrahydropyrido[3,4-e]-[1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one from Example 9 (15.4 g) in 2-methoxyethanol (145 ml) and 4 normal aqueous sodium hydroxide (73 ml) is stirred under nitrogen at 120° for 16 hours. The cooled reaction mixture is gradually brought to pH with dilute hydrochloric acid under stirring. The solid material is collected, recrystallized from 2-methoxypropanol and dried in vacuo at 100° for 20° hours. The pure 2-(2-fluorophenyl)-7,8,9,10-tetrahydropyrido[3,4-e]-[1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one thus obtained melts in the range from 254-257° (68 % yield).

Example 16: By the method described in Example 15, 2-(2-furyl)-7,8,9,10-tetrahydropyrido[3,4-e]-[1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one is obtained from the urethane of Example 14, melting in the range 240 to 245° (72 % yield).

Example 17: To a solution of 2-(2-fluorophenyl)-7,8,9,10-tetrahydropyrido[3,4-e]-[1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one (1.03 g, Example 15), triethylamine (0.9 ml) and 1-methyl-2-pyrrolidinone (18 ml) under nitrogen and magnetic stirring in an ice bath is added benzoyl chloride (0.83 g). It is stirred at room temperature for 48 hours, then diluted with water and extracted with ethyl acetate. The insoluble material is collected, washed with ether and air dried to afford pure 9-benzoyl-2-(2-fluorophenyl)-7,8,9,10-tetrahydropyrido[3,4-e]-[1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one, in 83 % yield, melting at 342 to 344°.

Example 18: A mixture of 2-(2-fluorophenyl)-7,8,9,10-tetrahydropyrido[3,4-e]-[1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one (80.57 g, Example 15) and phenylacetylchloride (3 ml) is heated under nitrogen at 120° for 4 hours. The mixture is diluted with ether (30 ml) and the solid collected, washed with ether and air dried to afford pure 9-phenylacetyl-2-(2-fluorophenyl)-7,8,9,10-tetrahydropyrido[3,4-e]-[1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one, mp 310-313°, in 85 % yield.

Example 19: A mixture of 2-(2-fluorophenyl)-7,8,9,10-tetrahydropyrido[3,4-e]-[1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one (0.57 g, Example 15) and phenylisocyanate (3 ml) is heated at 120° for 4 hours, cooled and the resulting solid triturated with ether (30 ml), filtered, washed with ether and dried. The pure 9-phenylureido-2-(2-fluorophenyl)-7,8,9,10-tetrahydropyrido[3,4-e]-[1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one is thus obtained, mp 291-293°, in 89 % yield.

Example 20: A mixture of ethylcarbamate of N-methyl-3-cyano-4-amino- Δ^3 -piperidine (14.6 g), o-fluorobenzhydrazide (10.78 g), tri-n-propylamine (9.5 ml) and 2-methoxyethanol (230 ml) is stirred at reflux under nitrogen for 66 hours, cooled and concentrated to a small volume at reduced pressure. The residue is triturated with isopropanol and the resulting solid collected, washed with methanol and dried. The solid is taken up in methanol, treated with an equimolar quantity of methanesulphonic acid and the resulting salt collected and air dried in vacuo to afford pure 2-(2-fluorophenyl)-9-methyl-7,8,9,10-tetrahydropyrido[3,4-e]-[1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one methanesulphonate, mp 285-287°, in 41 % yield.

The starting material is prepared by the method described in Example 2 from N-methyl-3-cyano-4- Δ^3 -piperidine, prepared as described by Cologne et al., Bull. Soc. Chim. France, 1963, 2264-2270, in 86 % yield.

Example 21: When the ethyl carbamate of N-ethyl-3-cyano-4-amino- Δ^3 -piperidine is substituted for the N-methyl compound of Example 20, 9-ethyl-2-(2-fluorophenyl)-7,8,9,10-tetrahydropyrido[3,4-e]-[1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one methanesulphonate is obtained, mp 184-286°, in 48 % yield.

The ethyl carbamate is prepared by the method described in Example 2 from N-ethyl-3-cyano-4- Δ^3 -piperideine, prepared as described by Cologne et al., Bull. Soc. Chim. France, 1963, 2264-2270, in 81 % yield.

Example 22: When the ethyl carbamate of N-isopropyl-3-cyano-4-amino- Δ^3 -piperideine is substituted for the N-methyl compound of Example 20, 2-(2-fluorophenyl)-9-isopropyl-7,8,9,10-tetrahydropyrido[3,4-e][1,2,4]triazolo[1,5-c]-pyrimidin-5-(6H)one methanesulphonate is obtained, mp 300-303°, in 62 % yield.

The ethyl carbamate used as starting material is prepared from N-isopropyl-3-cyano-amino-4- Δ^3 -piperideine as described in Example 2. This amino compound is prepared from N-isopropyl bis-(β -cyanoethyl)amine as described by Cologne et al., Bull. Soc. Chim. France, 1963, 2264-2270. The amine is prepared by reaction of isopropylamine in water with two moles of acrylonitrile at ambient temperature over 4 days in almost quantitative yield. The material is extracted with ether, the ether solution dried over magnesium sulphate and concentrated to a heavy oil. All intermediates are oils and require no further purification.

Example 23: When the ethyl carbamate of N- β -phenethyl-3-cyano-4-amino- Δ^3 -piperideine is substituted for the N-methyl compound in Example 20, 2-(2-fluorophenyl)-9- β -phenethyl-7,8,9,10-tetrahydropyrido[3,4-e][1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one methanesulphonate is obtained, mp 167-171°, in 38 % yield.

The ethyl carbamate starting material was prepared in the same manner as the ethyl carbamate in Example 22, except that β -phenethylamine is substituted for isopropylamine.

Example 24: When the ethyl carbamate of 1-benzyl-3-amino-4-cyano-2-methyl- Δ^3 -pyrroline is substituted for the ethyl carbamate of the N-benzyl compound in Example 11, 8-benzyl-2-(2-fluorophenyl)-7-methyl-7,9-dihydro-8H-pyrrolo[3,4-e][1,2,4]triazolo[1,5-c]-pyrimidin-5-(6H)one is obtained, mp 290-293°, after recrystallization from 2-methoxyethanol, in 36 % yield.

The ethyl carbamate intermediate is prepared from 3-amino-1-benzyl-4-cyano-2-methyl- Δ^3 -pyrroline (Cavalla, J. Chem. Soc. 1962, 4664) as described in Example 2.

Example 25: A mixture of the ethyl carbamate of 1-amino-2-cyano-cyclohept-1-ene (11.6 g), o-fluorobenzhydrazide (8.74 g) and 1-methyl-2-pyrrolidone (140 ml) is stirred at reflux under nitrogen for 18 hours, cooled and triturated with water to produce solid material. It is recrystallized from (\pm) 1-methoxy-2-propanol to afford pure 2-(2-fluorophenyl)-8,9,10,11-tetrahydro-7H-cyclohepta[e][1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one, mp 257-259°, in 63 % yield.

The starting material ethyl carbamate is prepared from 1-amino-2-cyanocyclohept-1-ene (Krüger, J. Organometal. Chem. 9, 125 (1967) as described in Example 2.

Example 26: A mixture of ethyl carbamate of 4-amino-3-cyanopyridine (81.3 g), o-fluorobenzhydrazide (1.05 g), 2-methoxyethanol (15 ml) and tri-n-propylamine (0.9 ml) is heated at reflux under nitrogen for 66 hours. One-half of the solvent is removed by evaporation at reduced pressure and the mixture is then cooled, filtered and the precipitate washed with ethanol and dried. After recrystallization from dimethylacetamide-ethanol, it is treated with an equimolar quantity of methanesulphonic acid in methanol and the salt precipitates by addition of ether. The product, (43 %) 2-(2-fluorophenyl)-pyrido[3,4-e][1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one methanesulphonate, melts in the range 290 to 293°.

The starting material ethyl carbamate is prepared in the following way: To a heterogeneous mixture of 4-amino-3-cyanopyridine (1.2 g), sodium bicarbonate (1.9 g) and methyl ethyl ketone (30 ml) is added under nitrogen and stirring ethyl chloroformate (1.9 ml). It is refluxed under nitrogen for 20 hours, filtered free of inorganic solid and the filtrate concentrated at reduced pressure. The residual solid is recrystallized from chlorobenzene-cyclohexane to give the desired carbamate, melting in the range 108-120°. This is suitable for the next step.

Example 27: The methyl carbamate of 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo(b)thiophene (7.08 g), 2-fluorobenzhydrazide (4.66 g), 2-methoxyethanol (100 ml) and tri-n-propylamine (3 ml) are refluxed under nitrogen for 19 hours. The mixture is cooled and the precipitate collected. The mother liquor is treated with methanol (100 ml) and refrigerated 24 hours to produce a second crop of solid. The combined material is recrystallized from 2-methoxyethanol and dried 20 hours at 100°/0.01 mm to afford 2-(2-fluorophenyl)-8,9,10,11-tetrahydro(1)benzothieno[3,4-e][1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one, which decomposes above 316°. The yield is 50 %.

The starting material carbamate is prepared in the following way: To a solution of 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo(b)thiophene (8.9 g, prepared as described by Gewald et al., Chem. Ber. 99, 94 (1966)), in methyl ethyl ketone (150 ml) is added sodium bicarbonate (5 g) followed by methyl chloroformate (4.2 ml) and the whole stirred at 80° under nitrogen for 20 hours. It is filtered free of inorganic solid while hot and the filtrate concentrated to dryness at reduced pressure. The residue is recrystallized from chlorobenzene-cyclohexane to afford the pure methyl carbamate, mp 162-164°, in 66 % yield.

Example 28: When the methyl carbamate of 2-amino-3-cyano-4,5-dimethylthiophene is substituted for the carbamate in Example 27, 2-(2-fluorophenyl)-8,9-dimethylthieno[3,4-e][1,2,4]triazolo[1,5-c]pyrimidin-5(6H)one is obtained, which decomposes above 330°, in 83 % yield.

The starting methyl carbamate is obtained from the aminonitrile (prepared by the method of Gewald et al., loc. cit.) as described in Example 27., mp 155-157° after recrystallization.

Example 29: In a pressure vessel is placed 30 ml of ammonium hydroxide saturated with ammonia at 0° and 5-chloro-2-(2-furyl)-7,8,9,10-tetrahydro[1,2,4]triazolo[1,5-c]quinazoline (0.63 g) and the whole is heated at

150° for 6 hours. The mixture is cooled and the precipitate collected, washed with methanol and recrystallized from 2-methoxyethanol. The free base is converted with methanesulphonic acid in isopropanol to the salt and precipitated with ether. The pure 5-amino-2-(2-furyl)-7,8,9,10-tetrahydro[1,2,4]triazolo[1,5-c]quinazoline methane sulphonate melts in the range 269 to 271°. It is obtained in 38 % yield.

5 The starting chloro compound is prepared as follows:

To a solution of phosphorous pentachloride (0.1 g) in phosphoryl chloride (13.7 ml) is added 2-(2-furyl)-7,8,9,10-tetrahydro[1,2,4]triazolo[1,5-c]quinazolin-5(6H)one (Example 3, 0.64 g), the mixture stirred for 5 minutes and pyridine (0.41 g) added dropwise. It is heated at 110° for 17 hours and then concentrated to dryness at reduced pressure. The residual solid is suspended in ethyl acetate (100 ml) and the mixture washed
10 with cold 2N hydrochloric acid (3 x 30 ml). The organic layer is dried over sodium sulphate and concentrated to dryness at reduced pressure to yield a white solid suitable for the next step, in 93 % yield.

Example 30: A mixture of 3-(5-aminoimidazol-4-yl)-5-phenyl-1,2,4 triazole (11.3 g, from Example 1), methanol (200 ml) and cyanogen bromide (5.25 g) is stirred under nitrogen for 2 hours at 40°. It is cooled and the solid collected, dissolved in 10 N sodium hydroxide solution, filtered and precipitated by addition of glacial
15 acetic acid to pH 5. The solid is washed with water, stirred in a mixture of methanesulphonic acid in methanol for one-half hour and collected (1.39 g), mp >350°. After drying at room temperature and high vacuum, the hemihydrate of 5-amino-2-phenyl-[1,2,4]triazolo[5,1-i]-purine is thus obtained.

Flunitrazepam binding studies were undertaken with the compounds of Examples 1, 2, 4-9, 13 and 15-50. The results thereof are set forth in the Table below as IC₅₀ in nanomolar values.

20

25

30

35

40

45

50

55

60

65

Compound of Example #	Flunitrazepam Binding	
1	> 1000	5
2	1.7	10
4	> 1000	
5	> 20	
6	4.7	15
7	22.7	
8	0.44	
9	13.3	20
13	2.4	
15	440	
16	> 1000	25
17	50	
18	140	
19	67	30
20	180	
21	150	
22	110	35
23	28	
24	> 1000	
25	10	40
26	12	
27	> 20	
28	> 20	45
29	1000	
30	> 1000	50

Example 31: A mixture of 2-(2-fluorophenyl)-7,8,9,10-tetrahydro[1,2,4]triazolo[1,5-c]quinazolin-5(6H)one, (Example 2, 1.4 g), and sodium methoxide (400 mg) is dissolved in dry dimethylsulphoxide (80 ml) under nitrogen at 85°. stirred at 50° for 30 min. and then treated dropwise with methyl iodide (0.7 ml) in dimethylsulphoxide (20 ml). It is allowed to stir another hour at 50°, then quenched in ice-water and the resulting white precipitate collected, washed with water and dried at 100° under vacuum. It is recrystallized from 2-methoxyethanol to afford pure 2-(2-fluorophenyl)-6-methyl-7,8,9,10-tetrahydro[1,2,4]triazolo[1,5-c]quinazolin-5(6H)one, mp 236-239°. 55

Example 32: To a suspension of 50 % sodium hydride in oil (300 mg) in dry dimethylformamide (16 ml) is added 3-(2-amino-pyrazin-3-yl)-5-(2-furyl)-1,2,4-triazole (1.37 g) and the whole stirred under nitrogen at 60° until a solution forms. To this is added cyanogen bromide (700 mg) in dimethylformamide (9 ml) and the whole stirred under nitrogen over 66 hours at 60°. It is cooled to 0° and the solid collected, washed with dimethylformamide, water, then ethanol and finally ether and air dried. It is recrystallized from dimethylacetamide (70 ml) to which methanol (50 ml) is added to form pure 5-amino-2-(2-furyl)-pyrazino[2,3-e][1,2,4]-triazolo[1,5-c]-pyrimidine, melting in the range 347-351°. 60

The starting material triazole is prepared in the following manner: To a suspension of sodium ethoxide, 65

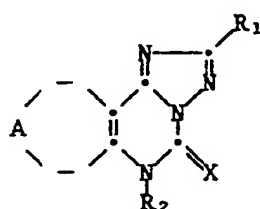
prepared from sodium (460 mg) in dry ethanol (20 ml) is added 2-furlycarboxamidine hydrochloride (2.9 g) in ethanol (20 ml) under nitrogen and after 5 min. stirring it is filtered and the filtrate added to a mixture of 2-aminopyrazine-3-carbohydrazide (3.1 g), ethanol (10 ml) and chlorobenzene (40 ml). It is heated under nitrogen in an apparatus with a solvent separator at 120° until no more solvent distills, then heated 18 hours at reflux. The mixture is cooled, filtered and the solid washed with methanol (3 x 30 ml) and recrystallized from 2-methoxyethanol to afford the pure triazole, mp 247-250°.

The starting material hydrazide is prepared by reaction of methyl-2-aminopyrazine-3-carboxylate with hydrazine hydrate at 80° for 1 hour. The methyl ester is prepared by reaction of 2-aminopyrazine-3-carboxylic acid with methanol containing concentrated sulphuric acid over 3 days, mp 167-170°.

Claims

Claims (for all designated contracting states except Austria):

1. A compound of the formula



(Ia)

its tautomers and pharmaceutically acceptable salts

wherein

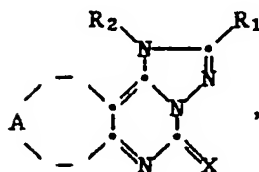
X is O, S, NH or NR;

R is lower alkyl, lower alkenyl, lower alkynyl, wherein the unsaturated bonds of the alkenyl and alkynyl groups are separated from the N Atom of X by at least one saturated carbon atom, cycloalkyl or aromatic ring-alkyl, all of the foregoing R alkyl groups being optionally interrupted by a hetero atom selected from O, N or S; or R is OH, hydroxy-C₂-C₄-alkyl, an aromatic ring, or the group -C(=NH)-NH₂;

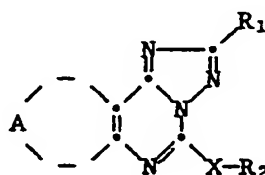
R₁ is optionally substituted and selected from a carbocyclic aromatic and a heterocyclic group, which heterocyclic group is aromatic, partially saturated or totally saturated, wherein the optional substituent of R₁ is selected from halogen, lower alkyl, haloalkyl, hydroxy, lower alkoxy, hydroxy-lower alkyl, amino, mono- and di-lower alkyl amino, carbalkoxy, carbamoyl and alkylcarbamoyl.

A is a bivalent bridging group containing chain atoms selected from C, O, N and S thus forming together with the two adjacent carbon atoms to which the chain is attached a mono- or bicyclic carbocyclic or heterocyclic group with the proviso that a monocyclic group formed by A is saturated or partially saturated and that the ring moiety adjacent to the triazolopyrimidine structure in a bicyclic, carbocyclic or heterocyclic group is other than carbocyclic aromatic, and A is optionally substituted by substituents from the group consisting of lower alkyl, lower alkoxy, OH, halogen, halo-lower alkyl, NO₂, NH₂, lower alkylthio, lower alkylsulfonyl, lower alkylsulfinyl, aryl-lower alkyl, amido, carbamoyl, carbo-lower alkoxy or aroyl.

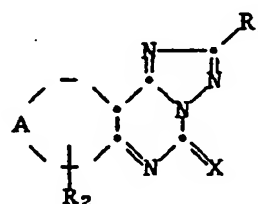
2. The tautomers of a compound of the formula Ia represented by the formulae:



(Ib)



(Ic)



(Id)

3. A compound according to claims 1 or 2, of the formulae Ia-Ic, wherein X represents O, S, NH or NR; R is lower alkyl, aryl-lower alkyl, amino-lower alkyl, or lower alkylamino-lower alkyl, R₁ represents phenyl or phenyl substituted by one to three groups selected from lower alkyl, lower alkoxy, hydroxy, halogeno and trifluoromethyl; or R₁ represents a heterocyclic radical bonded by way of a carbon atom, said heterocyclic

radical being a five or six membered ring which is aromatic or saturated either partially or totally; the heterocyclic group being unsubstituted or substituted by hydroxy, lower alkyl or halogen; and wherein R₂ represents hydrogen, lower alkyl, aryl-lower alkyl, lower alkenyl, aryl-lower alkenyl, or aryl; A is a bivalent bridging group of atoms selected from C, N, O, and S which form together with the two adjacent carbon atoms to which they are attached an optionally substituted, mono- or bicyclic aliphatic carbocyclic, or a heterocyclic ring or an optionally substituted mono- or bicyclic heteroatomic ring, the optional substituents of which are selected from lower alkyl, lower alkoxy, hydroxy, halogen, halo (preferably fluoro)-lower alkyl, lower alkylthio, lower alkylsulfonyl, lower alkylsulfinyl, aryl-lower alkyl, amido, carbonyl, carbo-lower alkoxy, and aroyl; and pharmaceutically acceptable salts thereof.

4. A compound according to claims 1 or 2 of the formulae Ia-Ic, wherein X represents O, especially when R₂ represents phenyl or substituted phenyl, NH or NR wherein R represents lower alkyl, especially when R₁ represents an aromatic heterocyclic group or a substituted aromatic heterocyclic group, R₁ represents phenyl or phenyl substituted by one to three groups selected from lower alkyl, for example methyl or ethyl; lower alkoxy, for example methoxy; hydroxy; halogeno, for example fluoro or chloro; and trifluoromethyl; or a 5- or 6- membered aromatic heterocyclic radical bonded by way of a ring carbon atom; for example 2- or 3-thienyl; 2- or 3-furyl; 2- or 3-pyrrolyl; 2-, 3- or 4-pyridyl; 3- or 4-pyrazolyl, or 2- or 4-(imidazolyl); said aromatic heterocyclic radical being unsubstituted or substituted by hydroxy; by lower alkyl, for example methyl or ethyl; or by halogeno, for example fluoro or by chloro, R₂ represents hydrogen or lower alkyl, A has a sufficient number of chain atoms to complete, together with the two carbon atoms of the triazolopyrimidine, a cyclohexene, cyclopentene, piperidine (especially -Δ³-piperidine), tetrahydrobenzo[b]thiophene (especially 1,2,3,4-tetrahydrobenzo[b]thiophene), pyridine, cycloheptene, dihydropyrrole (especially 2,5-dihydropyrrole), isoxazole, oxazole, isothiazole, thiazole, pyrazole, oxthiazole, dithiazole, pyrrole, furan, thiophene, oxazine, thiazine, pyridazine, pyran, thiopyrane, oxathiin, dioxine, dithiine, pyrazine, pyrimidine or imidazole group and benzocondensated and/or partially saturated benzocondensated derivatives, and the optional substituents of which are selected from lower alkyl, lower alkoxy, halo-lower alkyl, aryl-lower alkyl or carbo-lower alkoxy, and pharmaceutically acceptable salts thereof.

5. A compound according to claims 1 or 2 of the formulae Ia-Ic wherein R₁ represents phenyl or phenyl substituted by halogeno especially in the ortho or meta positions, particularly fluoro or chloro; or furyl, especially 2-furyl; R₂ represents hydrogen; X represents oxygen, especially when R₁ represents phenyl substituted by halogeno, for example ortho or meta fluoro; or X represents NH, especially when R₁ is 2-furyl; and A is a bivalent bridging group of atoms selected from C, N, O, and S which form together with the two adjacent carbon atoms to which they are attached a cyclohexene, cyclopentene, piperidine (especially -Δ³-piperidine), tetrahydrobenzo[b]thiophene (especially 1,2,3,4-tetrahydrobenzo[b]thiophene), pyridine, cycloheptene, dihydropyrrole (especially 2,5-dihydropyrrole), pyrazine, pyrimidine or imidazole group, and the optional substituents of which are selected from lower alkyl, lower alkoxy, halo-lower alkyl, aryl-lower alkyl or carbo-lower alkoxy, and pharmaceutically acceptable salts thereof.

6. A compound of the formula Ia wherein (1) the group A is -(CH₂)₅-, X is oxygen, R₁ is fluorophenyl, and (2) A is -(CH₂)₄-, X is NH and R₁ is furan-2-yl and pharmaceutically acceptable salts thereof.

7. 9-Benzyl-2-phenyl-7,8,9,10-tetrahydropyrido[3,4-e][1,2,4]-triazolo[1,5-c]pyrimidine-5(6H)one and pharmaceutically acceptable salts thereof.

8. 9-Benzyl-2-(3-fluorophenyl)-7,8,9,10-tetrahydropyrido[3,4-e][1,2,4] triazolo[1,5-c]pyrimidine-5(6H)one and pharmaceutically acceptable salts thereof.

9. Pharmaceutical compositions containing compounds of the formula I together with a pharmaceutically acceptable carrier.

10. The compounds according to claims 1 - 8 for use in the treatment of humans or animals.

11. The compounds according to claims 1 - 8 for use as anxiomodulators.

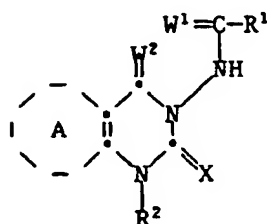
12. The compounds according to claims 1 - 8 for use as benzodiazepine antagonists.

13. Use of the compounds according to claims 1 - 8 for the preparation of pharmaceutical compositions.

14. Process for the preparation of pharmaceutical compositions according to claims 9 characterized by admixing a compound according to claim 1 with a pharmaceutical carrier material.

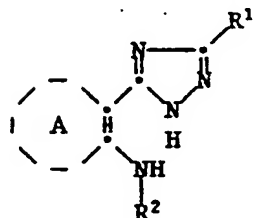
15. Process for the preparation of a compound according to claim 1 wherein the groups are as defined in claim 1, which comprises

a) cyclizing a compound of the formula:



(II),

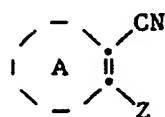
wherein R^1 , R^2 , X and ring A are as defined above, one of W^1 and W^2 is NH and the other one of W^1 and W^2 represents O or NH, by treatment with a base furnishing a nitrogen atom, or
b) cyclizing a compound of the formula:



(III),

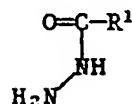
15 wherein R^1 , R^2 and ring A are as defined above, by treatment with a reactive derivative of carbonic acid, or

c) to obtain a compound wherein R_2 is hydrogen reacting a compound of the formula:



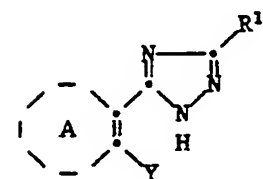
(IV)

25 wherein ring A is as defined above and Z is the radical of a carbonic acid derivative bonded via a nitrogen atom, with a hydrazide of the formula:



(V)

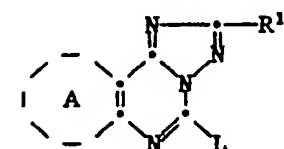
35 or d) to obtain a compound of formula I wherein R^2 represents hydrogen and X is oxygen, by treating a compound of the formula:



(VI),

wherein Y represents a group capable of being converted to the grouping $-N=C=O$ by an oxidizing agent, with said oxidizing agent followed by ring closure, or

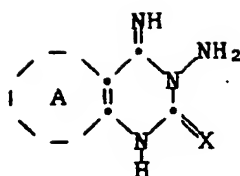
50 e) to obtain a compound of formula I, wherein R^2 is hydrogen and X is NH, converting a compound of the formula:



(VII),

60 wherein L is selected from halogen, lower alkoxy, aryl-lower alkoxy, mercapto, lower alkylthio and isothiocyanato, by replacing the group L by the grouping NH, or

f) to obtain a compound of formula I wherein R^2 represents hydrogen, by treating a compound of the formula:



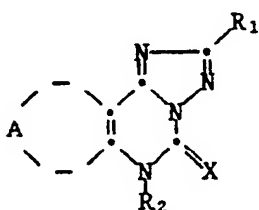
(VIII)

with a reactive derivative of a carboxylic acid of the formula $R^1\text{-COOH}$, and if desired, converting a resulting compound into another compound of the invention and/or converting a resulting salt into the free compound or into a different salt and/or converting a resulting free compound having a salt forming group into a salt.

16. The compounds obtainable by the process of claim 15.

Claims (for the contracting state Austria):

1. Process for the preparation of a compound of the formula



(Ia)

its tautomers and pharmaceutically acceptable salts
wherein

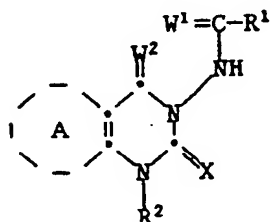
X is O, S, NH or NR;

R is lower alkyl, lower alkenyl, lower alkynyl, wherein the unsaturated bonds of the alkenyl and alkynyl groups are separated from the N Atom of X by at least one saturated carbon atom, cycloalkyl or aromatic ring-alkyl, all of the foregoing R alkyl groups being optionally interrupted by a hetero atom selected from O, N or S; or R is OH, hydroxy- $C_2\text{-}C_4$ -alkyl, an aromatic ring, or the group -C(=NH)-NH_2 ;

R_1 is optionally substituted and selected from a carbocyclic aromatic and a heterocyclic group, which heterocyclic group is aromatic, partially saturated or totally saturated, wherein the optional substituent of R_1 is selected from halogen, lower alkyl, haloalkyl, hydroxy, lower alkoxy, hydroxy-lower alkyl, amino, mono- and di-lower alkyl amino, carbalkoxy, carbamoyl and alkylcarbamoyl,

A is a bivalent bridging group containing chain atoms selected from C, O, N and S thus forming together with the two adjacent carbon atoms to which the chain is attached a mono- or bicyclic carbocyclic or heterocyclic group with the proviso that a monocyclic group formed by A is saturated or partially saturated and that the ring moiety adjacent to the triazopyrimidine structure in a bicyclic, carbocyclic or heterocyclic group is other than carbocyclic aromatic, and A is optionally substituted by substituents from the group consisting of lower alkyl, lower alkoxy, OH, halogen, halo-lower alkyl, NO_2 , NH_2 , lower alkylthio, lower alkylsulfonyl, lower alkylsulfinyl, aryl-lower alkyl, amido, carbamoyl, carbo-lower alkoxy or aroyl, which comprises

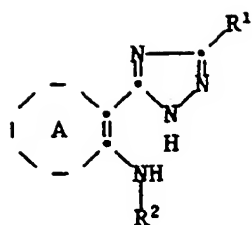
a) cyclizing a compound of the formula:



(II),

wherein R^1 , R^2 , X and ring A are as defined above, one of W^1 and W^2 is NH and the other one of W^1 and W^2 represents O or NH, by treatment with a base furnishing a nitrogen atom, or

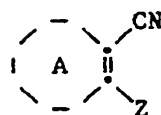
b) cyclizing a compound of the formula:



(III),

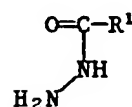
wherein R^1 , R^2 and ring A are as defined above, by treatment with a reactive derivative of carbonic acid, or

c) to obtain a compound wherein R_2 is hydrogen reacting a compound of the formula:



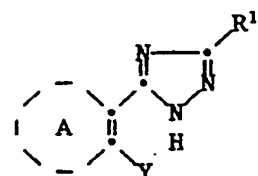
(IV)

wherein ring A is as defined above and Z is the radical of a carbonic acid derivative bonded via a nitrogen atom, with a hydrazide of the formula:



(V)

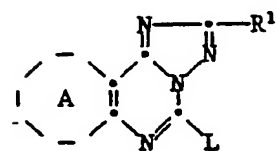
or d) to obtain a compound of formula I wherein R^2 represents hydrogen and X is oxygen, by treating a compound of the formula:



(VI),

wherein Y represents a group capable of being converted to the grouping $-N=C=O$ by an oxidizing agent, with said oxidizing agent followed by ring closure, or

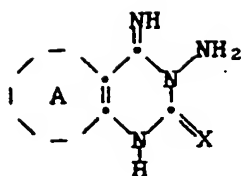
e) to obtain a compound of formula I, wherein R^2 is hydrogen and X is NH, converting a compound of the formula:



(VII),

wherein L is selected from halogen, lower alkoxy, aryl-lower alkoxy, mercapto, lower alkylthio and isothiocyanato, by replacing the group L by the grouping NH, or

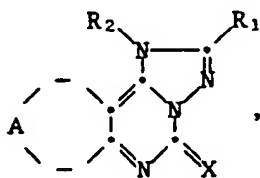
f) to obtain a compound of formula I wherein R^2 represents hydrogen, by treating a compound of the formula:



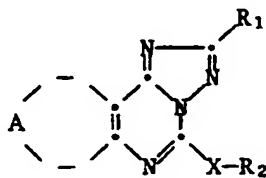
(VIII)

with a reactive derivative of a carboxylic acid of the formula $R^1\text{-COOH}$, and if desired, converting a resulting compound into another compound of the invention and/or converting a resulting salt into the free compound or into a different salt and/or converting a resulting free compound having a salt forming group into a salt.

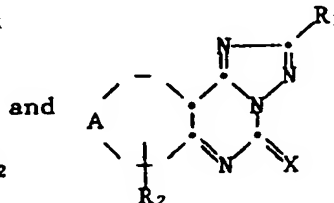
2. Process for the preparation of tautomers of a compound of the formula Ia represented by the formulae:



(Ib)



(Ic)



(Id)

characterised in that the process steps of claim 1 are carried out.

3. A process for the preparation of a compound according to claims 1 or 2, of the formulae Ia-Ic, wherein X represents O, S, NH or NR; R is lower alkyl, aryl-lower alkyl, amino-lower alkyl, or lower alkylamino-lower alkyl, R_1 represents phenyl or phenyl substituted by one to three groups selected from lower alkyl, lower alkoxy, hydroxy, halogeno and trifluoromethyl; or R_1 represents a heterocyclic radical bonded by way of a carbon atom, said heterocyclic radical being a five or six membered ring which is aromatic or saturated either partially or totally; the heterocyclic group being unsubstituted or substituted by hydroxy, lower alkyl or halogen; and wherein R_2 represents hydrogen, lower alkyl, aryl-lower alkyl, lower alkenyl, aryl-lower alkenyl, or aryl; A is a bivalent bridging group of atoms selected from C, N, O, and S which form together with the two adjacent carbon atoms to which they are attached an optionally substituted, mono- or bicyclic aliphatic carbocyclic, or a heterocyclic ring or an optionally substituted mono- or bicyclic heteroatomic ring, the optional substituents of which are selected from lower alkyl, lower alkoxy, hydroxy, halogen, halo (preferably fluoro)-lower alkyl, lower alkylthio, lower alkylsulfonyl, lower alkylsulfinyl, aryl-lower alkyl, amido, carbonyl, carbo-lower alkoxy, and aroyl; and pharmaceutically acceptable salts thereof, characterised in that the process steps of claim 1 are carried out.

4. A process for the preparation of a compound according to claims 1 or 2 of the formulae Ia-Ic, wherein X represents O, especially when R_2 represents phenyl or substituted phenyl, NH or NR wherein R represents lower alkyl, especially when R_1 represents an aromatic heterocyclic group or a substituted aromatic heterocyclic group, R_1 represents phenyl or phenyl substituted by one to three groups selected from lower alkyl, for example methyl or ethyl; lower alkoxy, for example methoxy; hydroxy; halogeno, for example fluoro or chloro; and trifluoromethyl; or a 5- or 6- membered aromatic heterocyclic radical bonded by way of a ring carbon atom; for example 2- or 3-thienyl; 2- or 3-furyl; 2- or 3-pyrrolyl; 2-, 3- or 4-pyridyl; 3- or 4-pyrazolyl, or 2- or 4-(imidazolyl); said aromatic heterocyclic radical being unsubstituted or substituted by hydroxy; by lower alkyl, for example methyl or ethyl; or by halogen, for example fluoro or by chloro, R_2 represents hydrogen or lower alkyl, A has a sufficient number of chain atoms to complete, together with the two carbon atoms of the triazopyrimidine, a cyclohexene, cyclopentene, piperidine (especially Δ^3 -piperidine), tetrahydrobenzo[b]thiophene (especially 1,2,3,4-tetrahydrobenzo[b]thiophene), pyridine, cycloheptene, dihydropyrrole (especially 2,5-dihydropyrrole), isoxazole, oxazole, isothiazole, thiazole, pyrazole, oxthiazole, dithiazole, pyrrole, furan, thiophene, oxazine, thiazine, pyridazine, pyran, thiopyrane, oxathiin, dioxine, dithiine, pyrazine, pyrimidine or imidazole group and benzocondensated and/or partially saturated benzocondensated derivatives, and the optional substituents of which are selected from lower alkyl, lower alkoxy, halo-lower alkyl, aryl-lower alkyl or carbo-lower alkoxy, and pharmaceutically acceptable salts thereof, characterised in that the process steps of claim 1 are carried out.

5. A process for the preparation of a compound according to claims 1 or 2 of the formulae Ia-Ic wherein R_1 represents phenyl or phenyl substituted by halogeno especially in the ortho or meta positions, particularly fluoro or chloro; or furyl, especially 2-furyl; R_2 represents hydrogen; X represents oxygen,

especially when R₁ represents phenyl substituted by halogeno, for example ortho or meta fluoro; or X represents NH, especially when R₁ is 2-furyl; and A is a bivalent bridging group of atoms selected from C, N, O, and S which form together with the two adjacent carbon atoms to which they are attached a cyclohexene, cyclopentene, piperidine (especially Δ^3 -piperidine), tetrahydrobenzo[b]thiophene (especially 1,2,3,4-tetrahydrobenzo[b]thiophene), pyridine, cycloheptene, dihydropyrrole (especially 2,5-dihydropyrrole), pyrazine, pyrimidine or imidazole group, and the optional substituents of which are selected from lower alkyl, lower alkoxy, halo-lower alkyl, aryl-lower alkyl or carbo-lower alkoxy, and pharmaceutically acceptable salts thereof.

6. A process for the preparation of a compound of the formula Ia wherein (1) the group A is $-(CH_2)_5-$, X is oxygen, R₁ is fluorophenyl, and (2) A is $-(CH_2)_4-$, X is NH and R₁ is furan-2-yl and pharmaceutically acceptable salts thereof.

7. A process for the preparation of a compound 9-Benzyl-2-phenyl-7,8,9,10-tetrahydropyrrodo[3,4-e][1,2,4]-triazolo[1,5-c]pyrimidin-5(6H)one and pharmaceutically acceptable salts thereof.

8. A process for the preparation of a compound 9-Benzyl-2-(3-fluorophenyl)-7,8,9,10-tetrahydropyrrodo[3,4-e][1,2,4] triazolo[1,5-c]pyrimidine-5(6H)one and pharmaceutically acceptable salts thereof.

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number:

**0 217 748
A3**

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: **86810421.7**(22) Date of filing: **25.09.86**

(51) Int. Cl.⁴: **C07D 487/04**, C07D 487/14 ,
C07D 471/14 , C07D 495/14 ,
C07D 498/14 , C07D 513/14 ,
C07D 493/14 , A61K 31/505 ,
A61K 31/535 , A61K 31/54 ,
//(C07D487/04,249:00,239:00),(-
C07D487/14,249:00,239:00,235-
:00),(C07D471/14,249:00,239:0-
0,221:00),(C07D487/14,249:00,-
239:00,209:00),(C07D495/14,33-
3:00,249:00,239:00)

(30) Priority: **30.09.85 US 782234**
20.03.86 US 841986

(43) Date of publication of application:
08.04.87 Bulletin 87/15

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

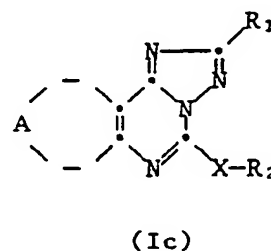
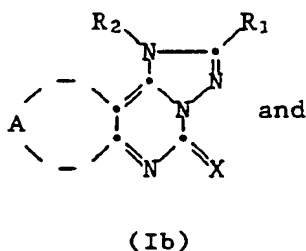
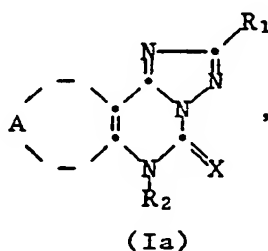
(88) Date of deferred publication of the search report:
07.01.88 Bulletin 88/01

(71) Applicant: **CIBA-GEIGY AG**
Klybeckstrasse 141
CH-4002 Basel(CH)

(72) Inventor: **Francis, John E., Dr.**
15 Wexford Way
Basking Ridge, NJ 07920(US)
Inventor: **Gelotte, Karl O.**
106 Stanie Brae Drive
Watchung, NH 07060(US)

(54) **2-Substituted-e-fused-[1,2,4,]triazolo-[1,5-c]pyrimidines pharmaceutical compositions and uses thereof.**

(57) Compounds of the formulae Ia, Ib and Ic



wherein

X is O, S, NH or NR;

R is alkyl, alkenyl, alkynyl, cycloalkyl, aromatic-ring-alkyl all of which may be optionally interrupted by a hetero atom; OH; an aromatic ring; or the group -C(=NH)-NH₂;

R₁ is optionally substituted and selected from a carboxylic aromatic and a heterocyclic group which heterocyclic group is aromatic, partially saturated or fully saturated, the optional substituent of R₁ being halogen, alkyl, haloalkyl, OH, alkoxy, hydroxyalkyl, amino, mono- or di-alkylamino, carbalkoxy, carbamoyl and alkylcarbamoyl;

R₂ is H, alkyl, hydroxy-C₂-C-alkyl, alkenyl, arylalkyl, or arylalkenyl;

A is a bivalent bridging group containing chain atoms selected from C, O, N and S thus forming together with the two adjacent carbon atoms to which the chain is attached a mono- or bicyclic carbocyclic or heterocyclic group with the proviso that a monocyclic group formed by A is saturated or partially saturated and that the ring moiety adjacent to the triazolopyrimidine structure in a bicyclic, carbocyclic or heterocyclic group is other than carbocyclic aromatic, and A is optionally substituted by substituents from the group consisting of alkyl, alkoxy, hydroxy, halogen, haloalkyl, NO₂, NH₂, lower alkylthio, lower alkylsulfonyl, lower alkylsulfinyl, aryl-lower alkyl, amido, carbamoyl, carbalkoxy or aroyl; and pharmaceutically acceptable salts thereof.



European Patent
Office

EUROPEAN SEARCH REPORT

Application number

DOCUMENTS CONSIDERED TO BE RELEVANT			EP 86810421.7
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
P, A	EP - A1 - O 181 282 (CIBA-GEIGY AG) * Claims 1,12-20 * --	1-16	C 07 D 487/04 C 07 D 487/14 C 07 D 471/14 C 07 D 495/14 C 07 D 498/14 C 07 D 513/14 C 07 D 491/14
A	EP - A1 - O 080 176 (BASF AKTIEN-GESELLSCHAFT) * Claims 1,9 * --	1-5,9, 10,13, 14	A 61 K 31/505 A 61 K 31/535 A 61 K 31/547 (C 07 D 487/04 C 07 D 249:00 C 07 D 239:00)
A	EP - A1 - O 023 773 (E.R.SQUIBB & SONS, INC.) * Claim 1 * --	1,15	(C 07 D 487/14 C 07 D 249:00 C 07 D 239:00 C 07 D 235:00)
A	DE - A - 2 261 095 (SANDOZ AG) * Claims 1,6 * --	1-5,9, 10,13- 16	(C 07 D 471/14 C 07 D 249:00 C 07 D 239:00 C 07 D 221:00)
D, A	MONATSHEFTE FÜR CHEMIE, vol. 106, 1975 F.SAUTER et al. "Synthese neuer Derivate des 2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-carbonitrils: basische Substitutionsprodukte und annelierte Thieno [1,2,4]-triazolo-pyrimidine" pages 1111-1116 * Page 1113 * -----	1,15	TECHNICAL FIELDS SEARCHED (Int. Cl. 4) C 07 D 487/00 C 07 D 471/00 C 07 D 495/00 C 07 D 513/00 C 07 D 498/00 C 07 D 491/00 C 07 D 497/00 C 07 D 515/00
The present search report has been drawn up for all claims			
Place of search VIENNA		Date of completion of the search 20-10-1987	Examiner PETROUSEK
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

EPO Form 1503 03/82



-2-

EP 86810421.7

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
			(C 07 D 487/14 C 07 D 249:00 C 07 D 239:00 C 07 D 209:00) (C 07 D 495/14 C 07 D 333:00 C 07 D 249:00 C 07 D 239:00)
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
The present search report has been drawn up for all claims			
Place of search VIENNA		Date of completion of the search 20-10-1987	Examiner PETROUSEK
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	